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PROCESS FOR PURIFYING (-)-Δ^9-TRANS-TETRAHYDROCANNABINOL

The present invention relates to a process for purifying (-)-Δ^9-trans-tetrahydrocannabinol. The compound is separated from a mixture of cannabinoids using a chromatographic technique.

(-)-Δ^9-trans-tetrahydrocannabinol is the active ingredient in marijuana. It is used therapeutically as an inhalant or an oral drug for stimulation of appetite among AIDS and cancer chemotherapy patients. Tetrahydrocannabinols (THCs) can be isolated from marijuana (a mixture of leaves and flowering heads of the plant *Cannabis Sativa*). Alternatively, THCs can be obtained by synthetic routes, e.g. as described in WO 02/096899. Enantiomerically pure THCs are required for formulation into drug products, but the purification of THCs, whether produced by isolation or synthesis, is challenging. The present inventors have sought to provide a process for providing enantiomerically pure (-)-Δ^9-trans-tetrahydrocannabinol ((-)-Δ^9-THC).

Chromatographic techniques have been used to separate (-)-Δ^9-THC from other cannabinoid compounds. The identification of cannabis products in drug samples has been achieved using Supercritical Fluid Chromatography. Such methods are described by Bäckström et al (Science & Justice, 1997, 37(2), 91-97), Cole ("Analysis of Cannabis by Supercritical Fluid Chromatography with Ultraviolet Detection", pages 145-148 in "Supercritical Fluid Methods and Protocols" ed. by Williams and Clifford), Veress (Journal of Chromatography A, 668 (1994), 285-291) and Later et al (Journal of Chromatographic Science, 1986, 24, 249-253). In these methods, very small samples (typically µg amounts) are analysed and the (-)-Δ^9-THC is often destroyed during the detection step (e.g. by flame ionisation detection or by chemical ionisation mass spectrometry). These chromatographic methods achieve separation of (-)-Δ^9-THC from other cannabinoid compounds, but are completely unsuitable for preparing sufficient quantities of enantiomerically pure (-)-Δ^9-THC for incorporation into pharmaceutical products.

Levin et al (Journal of Chromatography A, 654 (1993), 53-64) have developed an analytical procedure for separating enantiomeric mixtures of cannabinoid compounds. The chromatographic method uses a Daicel Chiralpak ® AD column, which is based on amylose tris(3,5-dimethylcarbamate) supported on macroporous silica gel. The mobile phase is n-hexane with ethanol or propanol. The enantioselective analysis determines the optical purity of samples but does not provide useful quantities of separated enantiomers.

Although chromatographic procedures have been used to analyse samples of cannabinoid compounds, an effective preparative separation of enantiomerically pure (-)-Δ^9-THC has not been demonstrated. The present inventors have devised a chromatographic process that can be used to prepare quantities of enantiomerically pure (-)-Δ^9-THC for incorporation into pharmaceutical products.

Accordingly, the present invention provides a preparative separation process wherein (-)-Δ^9-trans-tetrahydrocannabinol is separated from a mixture of cannabinoids, wherein the process comprises at least one chromatographic step wherein a mobile phase passes through a stationary phase, characterised in that the stationary phase comprises a derivatised polysaccharide and the mobile phase comprises carbon dioxide.

The inventors have found that a chromatographic process combining a derivatised polysaccharide stationary phase and a carbon dioxide-containing mobile phase provides an effective preparative separation of (-)-Δ^9-THC. By "preparative separation process" we mean a process that is capable of providing at least 0.1g of purified product, preferably at least 1g of purified product in a reasonable timeframe, i.e. less than a day.

Preferably the mobile phase in the present invention is a mixture of carbon dioxide and one or more modifiers. The modifier can be any liquid solvent such as an